1: J Cell Physiol 1998 May;175(2):141-8

Insulin-like growth factor-I promotes multidrug resistance in MCLM colon cancer cells.

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Insulin-like growth factor-I (IGF-I) is known as a potent mitogen for a variety of cell types, including colon cancer cell lines. The objective of this study was to determine the effect of IGF-I on cell death induced by cytotoxic agents actinomyci D (Act-D), lovastatin (LOV), and doxorubicin (DOX) in the MCLM mouse colon cancer cell line, and the mechanisms involved. Subconfluent monolayer MCLM cells were treated with IGF-I (25 ng/ml) for 12 h in serum-free media. Various concentrations of cytotoxic agents then were added to the cells that were incubated continually at 37 degrees C for 24 h Cell survival was determined with the MTT (3-[4-5-dimenthylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) assay, which assesses mitochondrial function in living cells. The mRNA expression for multidrug resistance gene-1 (mdr-1), c-H-ras, and manganese superoxide dismutase (MnSOD) in cells treated with IGF-I was examined by Northern blot or RNase protection assays. The levels of p-glycoprotein, a drug efflux pump encoded by the mdr-1 gene, were assessed by Western immunoblotting. Results demonstrated that 1) IGF-I significantly inhibited the cell death and apoptosis of MCLM cells treated with Act-D, LOV, or DOX; 2) IGF-I increased mRNA expression for mdr-1, c-H-ras, and MnSOD; 3) the p-glycoproteins in cells treated with IGF-I or stably transfected with c-H-ras were elevated when compared with control.

These results suggest that IGF-I protects MCLM cells against death induced by cytotoxic agents; this acquired drug resistance may be mediated by multiple mechanisms, including promoting expression of mdr-1, c-H-ras, and MnSOD; whereas, the p-glycoprotein level stimulated by IGF may result partly from the increase of c-H-ras in the cells.

PMID: 9525472 [PubMed - indexed for MEDLINE]

1: Anticancer Res 1994 Mar-Apr;14(2A):427-31

The effect of droloxifene on the insulin-like growth factor-I-stimulated growth of breast cancer cells.

Kawamura I, Lacey E, Mizota T, Tsujimoto S, Nishigaki F, Manda T, Shimomura K.

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Insulin-like growth factor-I (IGF-I) is an important mitogen in breast cancer. We studied here the effects of a new antiestrogen drug, droloxifene (DROL, (E)-alpha-[p-[2-(dimethylamino) ethoxy]-phenyl]-alpha'-ethyl-3-stilbenol) and tamoxifen (TAM) on the IGF-I-stimulated growth of estrogen receptor (ER) positive breast cancer cells, MCF-7 and their mechanism of action. IGF-I secretion from MCF-7 was increased by the addition of estrogen. Externally added IGF-I stimulated the growth of MCF-7 but not ER negative breast cancer cells, MDA-MB-231. DROL and TAM inhibited the IGF-I-stimulated growth of MCF-7. A 2 hr treatment with both drugs did not block IGF-I binding to the receptors in MCF-7. However, a 4 day treatment with DROL decreased the number of IGF-I receptors without altering the binding affinity in MCF-7. These results suggest that DROL can exert its antitumor activity against ER positive breast cancer not only by blocking the E2 binding to the ER, but also by counteracting the mitogenic effect of IGF-I.

PMID: 8017842 [PubMed - indexed for MEDLINE]

h cb hg e e e fcg c e e e b b e

1: Acta Oncol 1996;35 Suppl 5:19-22

Insulin-like growth factors in breast cancer.

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Insulin-like growth factor (IGF)-I is one of the most potent mitogens to many breast cancer cell lines in vitro. Effective growth inhibition in vitro may be achieved by antibodies to the type I IGF receptor (IGF-IR) or by using antisense strategies. Most human breast cancers express IGF-IR in vivo. Thus, different therapeutic strategies aimed at inhibiting ligand stimulation of the IGF-IR may be an attractive treatment option against breast cancer. Several drugs commonly used in breast cancer influence the IGF system both in vitro and in vivo. While antioestrogens such as tamoxifen and droloxifene reduce the expression of IGF-IR in vitro and suppress plasma levels of IGF-I but elevate IGF-binding protein-1 in vivo, megestrol acetate may reduce the delivery of IGFs to the tissues by inhibition of IGFBP-3 protease activity.

Publication Types:
- Review
- Review, Tutorial

PMID: 9142960 [PubMed - indexed for MEDLINE]

1: J Endocrinol 1997 Jan;152(1):39-47 Related Articles, Books, LinkOut

JOE Online

Activation of estrogen receptor-mediated gene transcription by IGF-I in human breast cancer cells.

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Estrogen and IGF-I are potent mitogens for most breast cancer cell lines, and although their signaling pathways contrast, there is considerable interaction between them. Recent evidence indicating that IGF-I can alter estrogen receptor (ER) action led us to investigate whether an inhibitor of IGF-I action. IGF-binding protein-1 (IGFBP-1), could affect transcriptional activation of ER. First, we confirmed that tamoxifen (TAM) could inhibit IGF-I-mediated proliferation of MCF-7 cells. Although TAM can increase IGFBP-3 expression in MCF-7 cells, and this binding protein has been shown to be able to inhibit IGF action, TAM had no effect on IGF-I-stimulated tyrosine phosphorylation of IGF-I receptor or the downstream signaling molecule, insulin receptor substrate-1. Therefore, to confirm that IGF-I was affecting transcriptional activation of ER, we utilized a gene reporter assay using a single consensus estrogen response element (ERE-tk-luc) upstream of luciferase. As expected, estradiol (E2; 1nM) increased transcriptional activation three- to fivefold from the ERE in three ER-positive breast cancer cell lines (MCF-7, ZR-75 and T47D). A 2.5-to 4-fold increase was also seen with IGF-I (5 nM). TAM (1 microM) effectively blocked activation by E2 and IGF-I, indicating disruption of ER-mediated transcription. As expected, human recombinant IGFBP-1 (80 nM) completely inhibited IGF-I-mediated activation of ER, however, IGFBP-1 also caused a significant decrease in E2-mediated activation. We also noticed that IGF-I increased the activity of all plasmids that we cotransfected including TATA-luc, SV40-luc and pGL Basic. This effect was post-transcriptional, as it was not affected by actinomycin D (2 micrograms/ml), while we were able to completely inhibit E2-mediated transcriptional activation of ERE-tk-luc. Unlike the complete inhibition of ER-mediated transcriptional activation by actinomycin D, IGF-I-mediated transactivation was reduced by only 50%, indicating that the activation by IGF-I represented both transcriptional and post-transcriptional effects. This study confirmed that IGF-I can cause transcriptional activation of

1: Eur J Cancer 1996 May;32A(5):842-8

Inhibition of insulin- and insulin-like growth factor-I-stimulated growth of human breast cancer cells by 1,25-dihydroxyvitamin D3 and the vitamin D3 analogue EB1089.

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1,25 Dihydroxyvitamin D3 (1,25-(OH)2D3) and a number of synthetic vitamin D3 analogues with low calcaemic activity, have been shown to inhibit breast cancer cell growth in vitro as well as in vivo. The purpose of the present study was to investigate a possible interaction of 1,25-(OH)2D3 and the vitamin D3 analogue EB1089 with the insulin-IGF-I regulatory system. The oestrogen receptor-positive MCF-7 human breast cancer cells used in this study are able to grow autonomously and their growth is stimulated by insulin. In order to avoid interference of IGF-binding proteins (IGF-BPs), we used an analogue of IGF-I, long R3 IGF-I, which stimulated MCF-7 cell growth similar to insulin. The growth stimulation by insulin and by long R3 IGF-I was completely inhibited by 1,25-(OH)2D3 and EB1089. Autonomous growth was also inhibited by 1,25-(OH)2D3 and EB1089. The analogue EB1089 was active at 50 times lower concentrations than 1,25-(OH)2D3. It was shown that growth inhibition was not achieved through downregulation of insulin and IGF-I binding after 48 h. Paradoxically, after prolonged treatment (8 days), an upregulation of insulin and IGF-I binding was observed. Two possible intracellular mediators of the insulin-IGF mitogenic signal are C-FOS and mitogen-activated protein (MAP) kinase. Insulin-induced C-FOS mRNA was inhibited by 1,25-(OH)2D3, suggesting that it could be involved in the growth inhibition by 1,25-(OH)2D3. MAP kinase activation appeared not to be involved in growth stimulation by both insulin and IGF-I. Together, the present study demonstrates that vitamin D3 compounds can block the mitogenic activity of insulin and IGF-I, which may contribute to their tumour suppressive activity observed in vivo.

PMID: 9081364 [PubMed - indexed for MEDLINE]

1: Recent Results Cancer Res 1998;152:63-70

IGF-I physiology and breast cancer.

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Recent studies imply that IGF-I levels vary greatly between normal women, and that premenopausal breast cancer risk is increased among women with higher IGF-I levels. It is known that tamoxifen lowers IGF-I levels, but further research is needed to determine whether antiestrogens will be of particular value in risk reduction for women with high IGF-I levels, and also to determine if IGF-I levels can indeed be used as an intermediate endpoint in risk reduction interventions. With respect to adjuvant therapy, we currently have convincing data that antiestrogens have moderate IGF-I lowering actions, but it remains unclear to what extent these contribute to the therapeutic effect of these compounds. Ongoing trials are addressing this question, as well as the hypothesis that interventions that increase IGF-I suppression will be associated with reduced relapse rates.

Publication Types:
- Review
- Review, Tutorial

PMID: 9928547 [PubMed - indexed for MEDLINE]

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1: Lancet 1998 May 9;351(9113):1393-6

Circulating concentrations of insulin-like growth factor-I and risk of breast cancer.

Hankinson SE, Willett WC, Colditz GA, Hunter DJ, Michaud DS, Deroo B, Rosner B, Speizer FE, Pollak M.

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BACKGROUND: Insulin-like growth factor (IGF)-I, a mitogenic and antiapoptotic peptide, can affect the proliferation of breast epithelial cells, and is thought to have a role in breast cancer. We hypothesised that high circulating IGF-I concentrations would be associated with an increased risk of breast cancer. METHODS: We carried out a nested case-control study within the prospective Nurses' Health Study cohort. Plasma concentrations of IGF-I and IGF binding protein 3 (IGFBP-3) were measured in blood samples collected in 1989-90. We identified 397 women who had a diagnosis of breast cancer after this date and 620 age-matched controls. IGF-I concentrations were compared by logistic regression with adjustment for other breast-cancer risk factors. FINDINGS: There was no association between IGF-I concentrations and breast-cancer risk among the whole study group. In postmenopausal women there was no association between IGF-I concentrations and breast-cancer risk (top vs bottom quintile of IGF-I, relative risk 0.85 [95% CI 0.53-1.39]). The relative risk of breast cancer among premenopausal women by IGF-I concentration (top vs bottom tertile) was 2.33 (1.06-5.16; p for trend 0.08). Among premenopausal women less than 50 years old at the time of blood collection, the relative risk was 4.58 (1.75-12.0; p for trend 0.02). After further adjustment for plasma IGFBP-3 concentrations these relative risks were 2.88 and 7.28, respectively. INTERPRETATION: A positive relation between circulating IGF-I concentration and risk of breast cancer was found among premenopausal but

1: Anticancer Res 1998 Mar-Apr;18(2A):1191-5

mRNA expression of components of the insulin-like growth factor system in breast cancer cell lines, tissues, and metastatic breast cancer cells.

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IGF-1 and 2 are thought to be important growth factors for breast cancer. However, gene expression of IGFs or IGF receptors in breast cancer tissues, and especially in metastatic breast cancer cells, is not well known. Expression of mRNA encoding for IGF-1, IGF-2, IGF-receptor 1 and 2, IGF binding proteins- 1 to -6, insulin receptor and insulin was determined in the NIH MCF-7 breast cancer cell line, in specimens from breast cancer tissues, and in 6 primary breast cancer cell cultures obtained from metastatic breast cancer, using rT-PCR technique. Specific mRNA sequences encoding for IGF-receptor 1 and 2, IGFBP-2, -4 and insulin receptor were identified in all cell cultures and most of the tissue specimens. Though in most of the tissues additional expression of IGF-1 and IGF-2 was detected, there was no mRNA encoding for these proteins in MCF-7 cell cultures as well as in the primary cell cultures of metastatic breast cancers. In none of our specimens mRNA encoding for IGFBP-1, -3, -5, -6 and insulin was detectable. IGF-receptor expression in cancer tissues and metastatic breast cancer cells supports the hypothesis that IGFs increase tumor cell proliferation in vivo. Expression of IGF-1 and IGF-2 in tumor tissues but not in cancer cell cultures indicates an IGF expression located predominantly in stromal parts of cancer tissues.

PMID: 9615787 [PubMed - indexed for MEDLINE]

Reduced testosterone, 17 beta-oestradiol and sexual hormone binding globulin, and increased insulin-like growth factor-1 concentrations, in healthy nulligravid women aged 19-25 years who were first and/or second degree relatives to breast cancer patients.

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Differences in hormonal and constitutional parameters between women with at least one first and/or second degree relative with breast cancer (RBC) and women without such affected relatives were studied in a group of healthy, nulligravid women aged 19-25 years. Present oral contraceptive (OC) users were analysed separately. In women not presently exposed to OCs we found significant correlations between RBC and reduced concentrations of testosterone during both the follicular ($P < 0.001$) and luteal menstrual cycle phases ($P = 0.016$). 17 beta-oestradiol was also significantly negatively correlated with RBC in the follicular ($P = 0.044$) and in the luteal phase ($P = 0.027$). RBC was significantly correlated with a lower waist/hip ratio ($P = 0.044$) compared with women without such a history. In multivariate analyses, the results for testosterone but not 17 beta-oestradiol remained significant. In these analyses high IGF-1 ($P = 0.05$) in the follicular phase and low sexual hormone-binding globulin (SHBG) ($P = 0.04$) in the luteal phase were also related to RBC. Including all 66 women in a multivariate model that analysed the specific effects from OCs and RBC on plasma testosterone showed that plasma testosterone was significantly lower among present OC users ($P = 0.004$) and in women with RBC ($P = 0.005$) during cycle days 5-10, with a significant positive two-way interaction between present OC use and RBC ($P = 0.007$). During cycle days 18-23 plasma testosterone showed a significant negative relationship with present OC use ($P < 0.001$) and RBC ($P = 0.016$) no significant interaction was seen during cycle days 18-23. Factors not significantly related to RBC were height, weight, breast size, age at menarche, p-progesterone and p-prolactin. It is concluded that a family history of breast cancer significantly lowered plasma testosterone concentrations in both cycle phases among healthy, nulligravid women compared with women without such history.

1: Oncology 1999 Nov;57(4):330-40

Plasma insulin-like growth factor-I and serum IGF-binding protein 3 can be associated with the progression of breast cancer, and predict the risk of recurrence and the probability of survival in African-American and Hispanic women.

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In vitro studies have shown that insulin-like growth factor (IGF) is a mitogen for breast cancer cells. However, the associations of plasma IGF-I with tumor histopathology in high-risk groups need further investigation. We hypothesize that plasma IGF-I and serum IGFBP3 concentrations in breast cancer patients may provide useful information on the progression of their disease, and determine the probability of recurrence and survival. We have carried out a retrospective study on 130 minority breast cancer patients. Plasma IGF-I and serum IGFBP3 were correlated with tumor histopathology, menopausal status, treatment modality, recurrence rates, and probability of survival. Plasma IGF-I and serum IGFBP3 were measured by radioimmunoassay. Our studies show that breast cancer patients have elevated plasma IGF-I and serum IGFBP3 levels. In addition we observed the following: IGF-I did not correlate with age and nodal stage. IGF-I and IGFBP3 increased with tumor size (T4). IGF-I did not correlate with estrogen receptor status, but did increase in progesterone-receptor-positive patients. IGF-I levels were higher in premenopausal patients and in women with cancer recurrence. Tamoxifen reduced IGF-I levels significantly and reduced the risk of recurrence. The survival probability was greater in patients with plasma IGF-I levels <120 ng/ml. In conclusion, lowering of plasma IGF-I may offer the following benefits: (a) reduce the risk of developing breast cancer in high-risk groups; (b) slow the progression of breast cancer in patients at early stages of cancer; (c) lower the risk of recurrence, and (d) increase the probability of survival.

1: Eur J Cancer 1999 Nov;35(12):1717-23

Vitamin D analogues suppress IGF-I signalling and promote apoptosis in breast cancer cells.

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Survival factors are known to promote cell viability, and factor deprivation can be a potent apoptotic signal. Insulin-like growth factors are potent mitogens and inhibitors of apoptosis for many normal and neoplastic cells with insulin-like growth factor-I (IGF-I) being the most effective in many breast cancer cell lines. 1,25-dihydroxyvitamin D3 (1,25(OH)2D3) and its analogues inhibit IGF-I-stimulated growth of MCF-7 human breast cancer cells. The aim of this study was to determine the relationship between inhibition of IGF-I responsiveness and induction of apoptosis by vitamin D analogues in breast cancer cells. Vitamin D analogues EB1089 and CB1093 inhibited autonomous and IGF-I-stimulated growth of MCF-7 and T47D cells and autonomous growth of IGF-I-insensitive Hs578T cells. In MCF-7 cells, IGF-I alone (4 nM) protected against apoptosis mediated by serum deprivation. Co-treatment with vitamin D analogues prevented the anti-apoptotic effects of IGF-I. In T47D cells, IGF-I treatment provided only partial protection against apoptosis induced by serum deprivation and co-incubation of serum-deprived cells with 100 nM CB1093 and IGF-I abrogated this partial protection. In Hs578T cells, addition of IGF-I did not prevent apoptosis induced by serum deprivation. However, treatment with CB1093 attenuated the protective effect of the serum in these cells. Our findings suggest that vitamin D analogues inhibit IGF-I signalling pathways to promote apoptosis in breast cancer cells.

PMID: 10674019 [PubMed - indexed for MEDLINE]

Insulin-like growth factor-I and human lung fibroblast-derived insulin-like growth factor-I stimulate the proliferation of human lung carcinoma cells in vitro.

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Department of Biochemistry and Nutrition, Virginia Polytechnic Institute and State University, Blacksburg 24061.

The concentration of insulin-like growth factor I (IGF-I) in tissue taken from human non-small cell lung carcinomas (non-SCLC) is 1.4- to 7-fold higher than in the surrounding normal lung tissue, and thus, IGF-I may be involved in the growth of non-SCLC. We report here that non-SCLC cell lines (A549, A427, SK-LU-1) expressed the IGF-I receptor protein, and IGF-I stimulated the proliferation of low-density plated (2000 cells/cm2 growth area) carcinoma cells by 1.6- to 3-fold above control after a 4-day incubation period under serum-free conditions (A549, A427) or in the presence of 0.25% serum (SK-LU-1). Immunoblot data indicated that IGF-I was not secreted by the lung carcinoma cells; however, IGF-I-like proteins were present in the serum-free medium conditioned by human adult lung fibroblasts (CCD-19Lu). The secretion of the immunoreactive IGF-I-like protein was dependent on the passage level of the fibroblasts. At least one of the IGF-I-like factors promoted the serum-free growth of A549 cells (2-fold increase in cell number over control after 4 days) and stimulated a 3-fold increase in the tyrosine kinase activity of detergent-solubilized IGF-I receptors from A549 cells. Both stimulatory effects were neutralized by an anti-IGF-I antibody, suggesting that the fibroblast-derived factor mediated its activity via the IGF-I receptor. Our data indicate that lung fibroblast-derived IGF-I may stimulate the growth of non-SCLC in vivo.

PMID: 8391925 [PubMed - indexed for MEDLINE]

1: Int J Biol Markers 1991 Apr-Jun;6(2):99-102

Blood levels of IGF-I in non-small cell lung cancer: relation to clinical data.

Tisi E, Lissoni P, Rovelli F, Mandelli D, Barni S, Tancini G.

Division of Thoracic Surgery, San Gerardo Hospital, Monza, Italy.

Recent observations have demonstrated that somatomedins, mainly insulin-like growth factor-I (IGF-I), are growth factors for non-small cell lung cancer (NSCLC). On the basis of this evidence, a study was started to evaluate serum levels of IGF-I in a group of untreated NSCLC patients. The study included 46 patients, 25 of whom had an operable tumor, while the other 21 showed distant organ metastases. IGF-I and GH serum levels were measured by RIA in each patient; moreover, in operable patients, hormonal detections were made either before, or 7 days after surgery. The control group comprised 38 age-matched healthy subjects. Mean serum levels of IGF-I were significantly higher in cancer patients with respect to controls, while no difference was seen in mean GH values. Moreover, patients with metastases showed significantly higher levels of IGF-I than the patients without. Within the operable group, patients with lung adenocarcinoma had higher levels of IGF-I than those with epidermoid cell carcinoma, but this difference was not significant. Finally, no significant difference in IGF-I mean values was seen before and after surgical removal of tumors. This preliminary study shows that NSCLC patients may present abnormally high levels of IGF-I. Because of the stimulating role of IGF-I on NSCLC growth, this evidence could play a role in the clinical course of neoplastic lung disease.

PMID: 1653807 [PubMed - indexed for MEDLINE]

Serum insulin-like growth factor-I levels in patients with small cell lung cancer.

Macaulay VM, Teale JD, Everard MJ, Joshi GP, Millar JL, Smith IE.

Publication Types:
- Letter

PMID: 2843377 [PubMed - indexed for MEDLINE]

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Somatomedin-C/insulin-like growth factor-I is a mitogen for human small cell lung cancer.

Macauly VM, Teale JD, Everard MJ, Joshi GP, Smith IE, Millar JL.

Department of Medicine, Royal Marsden Hospital, Sutton, Surrey, UK.

PMID: 2831929 [PubMed - indexed for MEDLINE]

h cb hg e e e fcg c e e e b b e

1: Anticancer Res 1999 Mar-Apr;19(2B):1397-9

Decreased serum levels of insulin-like growth factor (IGF)-I in patients with lung cancer: temporal relationship with growth hormone (GH) levels.

Mazzoccoli G, Giuliani A, Bianco G, De Cata A, Balzanelli M, Carella AM, La Viola M, Tarquini R.

Department of Internal Medicine, Regional General Hospital Casa Sollievo della Sofferenza, Italy.

AIMS AND BACKGROUND: Several studies have evidenced that IGF-1 may play a role in the growth regulation of many cancer cell lines, and recently GH and IGF-1 have been recognized as stimulators of lymphopoiesis and immune function. We investigated whether there are differences among health- old people and old people suffering from lung cancer at different stages of disease in the 24-hour secretory profiles of GH und IGF-1. METHODS: The study was carried out on seven healthy volunteers (mean age +/- s.e. 68.8 + 1.92), seven patients with I and II stage lung cancer (mean age +/- s.e. 67.2 +/- 0.80) and seven patients with III and IV stage lung cancer (mean age +/- s.e. 69.5 +/- 2.26). GH and IGF-1 serum levels were measured on blood samples collected every four hours for 24 hours; the area under the curve (AUC) and the presence of circadian rhythmicity were evaluated. RESULTS: A normal circadian rhythmicity was recognizable only for GH secretion in healthy subjects. A progressive increase of GH serum levels and a steady decrease of IGF-1 serum levels were observed in cancer patients in relation to advancing stage of neoplastic disease. CONCLUSIONS: Lung cancer is associated with an altered regulation of GH-IGF-1 system, that might play a role in the clinical course of neoplastic disease.

PMID: 10365112 [PubMed - indexed for MEDLINE]

h cb hg e e e fcg c e e e b b e

1: Br J Pharmacol 1997 Feb;120(3):537-43

Anti-insulin-like growth factor-I activity of a novel polysulphonated distamycin A derivative in human lung cancer cell lines.

de Cupis A, Ciomei M, Pirani P, Ferrera A, Ardizzoni A, Favoni RE.

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1. The purpose of this study was to investigate the antiproliferative effect and the modulation of the mitogenic insulin-like growth factor-I (IGF-I) system by FCE 26644 and FCE 27784, two polyanionic sulphonated distamycin A derivative compounds, on two human non-small cell lung cancer (N-SCLC) cell lines. 2. For cell growth studies the colorimetric MTT and the thymidine incorporation assays were performed; the presence of IGF-I and IGF-binding proteins in conditioned media was revealed by radioimmunoassay and Western ligand blot, respectively. Variations at the IGF-I-receptor level were tested by binding studies on cell monolayers. 3. A significant concentration- and time-dependent cytostatic activity of FCE 26644 (IC50 approximately 200 micrograms ml-1 at 72 h) compared to its analogue FCE 27784 (IC50 > 800 micrograms ml-1) was observed in both cell lines studied. The IGF-I-stimulated proliferation of the IGF-I-responsive A549 cell line was abolished by 24 h of FCE 26644 treatment whereas FCE 27784 was inactive. FCE 26644 increased (4 to 6 fold) the secretion of IGF-I-like material and reduced the IGF-I binding (IC50 > 100 micrograms ml-1) in both A549 and Ca-Lu-1 cell lines. FCE 26644 (100 micrograms ml-1) did not affect the KD (approximately 0.5 nM) but reduced the Bmax and the number of receptor sites (50%). 4. Our findings demonstrate that the ability to down-regulate the cell proliferation of N-SCLC cell lines, shown by FCE 26644, depends at least partially, on interference with the "IGF-I mitogenic system'.

PMID: 9031761 [PubMed - indexed for MEDLINE]

1: J Natl Cancer Inst 1999 Jan 20;91(2):151-6

Plasma levels of insulin-like growth factor-I and lung cancer risk: a case-control analysis.

Yu H, Spitz MR, Mistry J, Gu J, Hong WK, Wu X.

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BACKGROUND: Insulin-like growth factors (IGFs), in particular IGF-I and IGF-II, strongly stimulate the proliferation of a variety of cancer cells, including those from lung cancer. To examine the possible causal role of IGFs in lung cancer development, we compared plasma levels of IGF-I, IGF-II, and an IGF-binding protein (IGFBP-3) in patients with newly diagnosed lung cancer and in control subjects. METHODS: From an ongoing hospital-based, case-control study, we selected 204 consecutive patients with histologically confirmed, primary lung cancer and 218 control subjects who were matched to the case patients by age, sex, race, and smoking status. IGF-I, IGF-II, and IGFBP-3 plasma levels were measured by enzyme-linked immunosorbent assay and then divided into quartiles, based on their distribution in the control subjects. Associations between the IGF variables and lung cancer risk were estimated by use of odds ratios (ORs). Reported P values are two-sided. RESULTS: IGF and IGFBP-3 levels were positively correlated (all r>.27; all P<.001). High plasma levels of IGF-I were associated with an increased risk of lung cancer (OR = 2.06; 95% confidence interval [CI] = 1.19-3.56; P = .01), and this association was dose dependent in both univariate and multivariate analyses. Plasma IGFBP-3 showed no association with lung cancer risk unless adjusted for IGF-I level; when both of these variables were analyzed together, high plasma levels of IGFBP-3 were associated with reduced risk of lung cancer (OR = 0.48; 95% CI = 0.25-0.92; P = .03). IGF-II was not associated with lung cancer risk. CONCLUSIONS: Plasma levels of IGF-I are higher and plasma levels of IGFBP-3 are lower in patients with lung cancer than in control subjects. If these findings can be confirmed in prospective studies, measuring levels of IGF-I and IGFBP-3 in blood may prove useful in assessing lung cancer risk.

PMID: 9923856 [PubMed - indexed for MEDLINE]

Evidence for an increased somatomedin-C/insulin-like growth factor I content in primary human lung tumors.

Minuto F, Del Monte P, Barreca A, Fortini P, Cariola G, Catrambone G, Giordano G.

Immunoreactive somatomedin-C/insulin-like growth factor I (SM-C/IGF I) content was measured in human neoplastic lung tissue obtained from surgery on 10 patients (seven epidermoid carcinoma, three adenocarcinoma), and in normal lung tissue obtained from the same excised portion. SM-C/IGF I content in lung tumors was 615 +/- 123 (SE) milliunits/g of tissue (range, 214-1531), significantly higher (P less than 0.01) than normal tissue (234 +/- 51 milliunits/g of tissue; range, 37-537); in particular, every subject showed a clear-cut difference of SM-C/IGF I content between neoplastic and normal tissue (ratio, 3.41 +/- 0.69; range, 1.4-7.2). The results were essentially unchanged when data were expressed relative to hemoglobin or DNA tissue content. By contrast, in peripheral plasma SM-C/IGF I concentration was 0.51 +/- 0.17 units/ml, significantly lower (P less than 0.01) than in 59- to 70-yr-old control subjects (1.10 +/- 0.13 units/ml). In conclusion, the lung tumors studied, irrespective of their histological structure, contain more SM-C/IGF I than does normal tissue. Whether this is due to a primary in situ production of SM-C/IGF I or is secondary to overproduction of other inducers such as platelet derived growth factor-like peptides is yet to be clarified. The reduced circulating SM-C/IGF I concentration seems to be related more to the nutritional status of the patients.

PMID: 3940658 [PubMed - indexed for MEDLINE]

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1: Growth Horm IGF Res 1998 Dec;8 (6):473-9

Role of insulin-like growth factor-I (IGF-I) receptor, IGF-I, and IGF binding protein-2 in human colorectal cancers.

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The identification of novel autocrine/paracrine signaling pathways and possible markers represents an important component in the understanding of tumor growth control. In this study, we assessed the potential role of insulin-like growth factor-I (IGF-I), the IGF-I receptor (IGF-IR) and IGF binding protein-2 (IGFBP-2) in human colorectal cancer. Initi studies demonstrating increased IGF-I binding and IGF-IR density in human colon cancer tissue revealed that a component of iodinated (3-[125-I]iodotyrosyl) IGF-I (125I-ICGF-I) binding was not attributable to IGF-IR. Binding studies and Western blot analysis suggested that this second component of 125I-IGF-I binding could be due to IGFBP-2. Further analysis by a specific solution hybridization/RNase protection assay for IGF-IR mRNA levels, IGFBP-2 mRNA levels and in situ hybridization for IGFBP-2 localization, was carried out in nine patients with colon cancer. IGF-IR mRNA levels by RNAse protection assays were unchanged, whereas IGFBP-2 mRNA levels were increased 4-8-fold in patients witl colon cancer compared to controls. Three patients with Duke: stage C disease had the highest levels of IGFBP-2 mRNA. In situ hybridization studies localized IGFBP-2 mRNA to malignant cells and not to the surrounding stromal cells, suggesting an autocrine role for IGFBP-2. The discrepancy

between increased IGF-I binding, IGF-IR density, IGFBP-2 mRNA and the minimal modulation of the IGF-IR mRNA implies post-transcriptional regulation of IGF-IRs. Our results suggest that IGFBP-2 may be implicated in colon cancer metastases and prognosis. Its usefulness as a potential tumc marker should be further investigated.

PMID: 10985759 [PubMed - indexed for MEDLINE]

IGF-I and IGF-II in relation to colorectal cancer.

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Recent data suggest that the IGF system plays an important role in the pathogenesis of several forms of human cancer, and there is evidence that IGFs acting in an autocrine and paracrine manner may also affect colorectal cancer risk. We have conducted a case-control study on the island of Crete, Greece, to examine the potential relation between circulating IGF-I and -II and their major binding protein (IGF-BP3), on the one hand, and colorectal cancer, on the other. IGF-I, IGF II and IGF-BP3 were determined in the serum from 41 patients with colorectal cancer and 50 healthy controls; data were analyzed using unconditional multiple logistic regressior adjusting for age, gender, education, height and BMI, as well as mutually. Both IGF-I and IGF-II were positively, while IGF BP3 was inversely, associated with risk for colorectal cancer, though none of these relations reached statistical significance However, individuals with IGF-I and -II values in the upper 2 tertiles of the respective distributions had a significantly elevated odds ratio for colorectal cancer (OR = 5.2, 95% confidence interval 1.0-26.8) compared with those in the lower tertile in both distributions. Our results provide evidenc that high levels of circulating IGF-I and -II might be associated with colorectal cancer.

PMID: 10449601 [PubMed - indexed for MEDLINE]

1: Exp Cell Res 1999 Aug 25;251(1):22-32 Related Articles, Books, LinkC

ELSEVIER SCIENCE FULL-TEXT ARTICLE

Characterization of an antibody that can detect an activated IGF-I receptor in human cancers.

Rubini M, D'Ambrosio C, Carturan S, Yumet G, Catalano E, Shan S, Huang Z, Criscuolo M, Pifferi M, Baserga R.

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The type 1 insulin-like growth factor receptor (IGF-IR) plays an important role in malignant transformation and in apoptosis. Its role in human cancer has now been firmly established. IGF-IR signaling occurs only when the receptor i activated by its ligands, which induce autophosphorylation of the receptor at several tyrosine residues. Although the IGF-II (phosphorylated or not) can be detected in human cancers with conventional antibodies, it would be desirable to obtain antibodies that can detect the IGF-IR only when activated by its ligands. We describe and characterize in this paper such a antibody and show that it can be used in sections of human cancers to detect an autophosphorylated IGF-IR. This antibody will be useful in detecting autocrine or paracrine influences on normal and tumor cells and could eventually be also useful in diagnostic and prognostic studies of human primary and metastatic cancer. Copyright 1999 Academic Press.

PMID: 10438568 [PubMed - indexed for MEDLINE]

1: Cancer Res 1998 Sep 1;58(17):4008-14 Related Articles, Books, LinkC

Regulation of vascular endothelial growth factor expression in human colon cancer by insulin-like growth factor-I.

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We investigated the role of insulin-like growth factor (IGF)-I and IGF-binding proteins (IGFBPs) in the regulation of vascular endothelial growth factor (VEGF) expression in color cancer cells and the mechanism by which this regulation occurs. HT29 human colon cancer cells were treated with IGF I for various time periods. VEGF mRNA expression increased within 2 h and peaked at 24 h. SW620 colon cancer cells exhibited a peak induction of VEGF mRNA 8 h after IGF-I treatment. IGF-I induction of VEGF was confirmed at the protein level. In experiments using transient transfection of VEGF promoter-reporter constructs into HT29 cells, IGF-I increased the activity of the VEGF promoter, and pretreatment of HT29 cells with dactinomycin abrogated the induction of VEGF mRNA by IGF-I. The half-life of VEGF mRN was not prolonged by treatment with IGF-I. Blocking the activity of IGFBP-4 did not significantly modulate the effect o IGF-I induction of VEGF mRNA in HT29 cells. Treating cells with des-(1-3)-IGF-I (an active derivative of IGF-I that does not bind to binding proteins) had effects on VEGF mRNA expression that were similar to those of IGF-I. These findings suggest that IGF-I regulates VEGF expression in human color cancer cells by induction of transcription of the VEGF gene. IGFBPs do not significantly affect IGF-I induction of VEGF.

PMID: 9731515 [PubMed - indexed for MEDLINE]

☐ **1:** Int J Pept Protein Res 1993 May;41 (5):433-40

Three-dimensional structure of human insulin-like growth factor-I (IGF-I) determined by 1H-NMR and distance geometry.

Sato A, Nishimura S, Ohkubo T, Kyogoku Y, Koyama S, Kobayashi M, Yasuda T, Kobayashi Y.

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The three-dimensional structure of human insulin-like growth factor-I has been determined through a combination of NMR measurements and distance geometry calculations. A total of 320 interatomic distance constraints, including 12 related to the disulfide bridges, were used in these calculations. The resulting structure is characterized by the presence of three helical rods corresponding to the sequence regions, Ala8-Cys18, Gly42-Cys48 and Leu54-Cys61. Furthermore, a turn structure and an extended structure exist in the Gly19-Gly22 and Phe23-Asn26 regions, respectively. Neglecting the N- an C-termini, with their expectedly high degree of mobility as well as a fluctuating C-domain, the r.m.s.d. value is 1.9 A for backbone atoms. Those of the three alpha-helical regions are 1.0, 0.9 and 0.8 A, respectively, 1.8 A being that for the tota backbone atoms participating in the formation of these three helices, showing the good convergence of their spatial arrangements. The overall structure obtained here shows tha the human IGF-I molecule folds into a spatial structure very similar to that of insulin in an aqueous solution.

PMID: 8391516 [PubMed - indexed for MEDLINE]

☐ **1:** Protein Sci 1996 Nov;5 (11):2193-202

Solution structure of a mini IGF-1.

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Mini insulin-like growth factor 1, an inactive insulin-like growth factor 1 mutant lacking the C region, was studied by 2D NMR spectroscopy. Resonances were assigned for almost all protons of the 57 amino acid residues. The 3D structure o the protein was determined by distance geometry methods. Three helical segments; Ala 8-Cys 18, Gly 42-Phe 49, and Le 54-Cys 61, were identified, corresponding to those present ir wild-type insulin-like growth factor 1 and in single-chain insulin. Their relative orientation, however, was found to be changed. This change is connected with a displacement of th Phe 23-Tyr 24-Phe 25-Asn 26 beta-strand-like segment, i.e., of aromatic side chains known to be important for receptor binding. Thus, deletion of the C region of IGF-1 results in a substantial tertiary structural rearrangement that accounts fc the loss of receptor affinity.

PMID: 8931138 [PubMed - indexed for MEDLINE]

1: J Mol Biol 1995 Apr 28;248(2):385-401 Related Articles, Books, LinkC

ELSEVIER SCIENCE FULL-TEXT ARTICLE

Solution structure of human insulin-like growth factor II. Relationship to receptor and binding protein interactions.

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The three-dimensional structure of human insulin-like growth factor (IGF) II in aqueous solution at pH 3.1 and 300 K has been determined from nuclear magnetic resonance data and restrained molecular dynamics calculations. Structural constraints consisting of 502 NOE-derived distance constraints, 11 dihedral angle restraints, and three disulfide bridges were used as input for distance geometry calculations in DIANA and X-PLOR, followed by simulated annealing refinement and energy minimization in X-PLOR. The resulting family of 20 structures was well defined in the regions of residues 5 to 28 and 41 to 62, with an average pairwise root-mean-square deviation of 1.24 A for the backbone heavy-atoms (N, C2, C) and 1.90 A for all heavy atoms. The poorly defined regions consist of the N and C termini, part of the B-domain, and the C-domain loop. Resonances from these regions of the protein gave stronger cross peaks in two dimensional NMR spectra, consistent with significant motional averaging. The main secondary structure elements in IGF-II are alpha-helices encompassing residues 11 to 21, 42 to 49 and 53 to 59. A small anti-parallel beta-sheet is formed by residues 59 to 61 and 25 to 27, while residues 26 to 28 appear to participate in intermolecular beta-sheet formation. The structure of IGF-II in the well-defined regions is very

similar to those of the corresponding regions of insulin and IGF-I. Significant differences between IGF-II and IGF-I occur near the start of the third helix, in a region known to modulate affinity for the type 2 IGF receptor, and at the C terminus. The IGF II structure is discussed in relation to its binding sites for the insulin and IGF receptors and the IGF binding proteins.

PMID: 7739048 [PubMed - indexed for MEDLINE]
